REMARKS

FORMAL MATTERS:

Claims 48-91 are pending after entry of the amendments set forth herein.

Claims 48, 54, 55, and 84 are amended. Exemplary support for these amendments is found in claim 54 as previously presented (claim 48 and 84), and at page 23, lines 16-17 (claim 54).

Claim 55 is amended in view of the amendment to claim 48, from which it ultimately depends.

No new matter is added.

INFORMATION DISCLOSURE STATEMENT

Applicants request consideration of the references cited in the Information Disclosure Statement submitted with this amendment.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 48-91 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of copending U.S. application serial no. 11/044,521. This is a provisional rejection. Applicants respectfully request that this rejection be held in abeyance until the subject rejection is the sole remaining rejection in either the present application or in the 11/044,521 application.

REJECTIONS UNDER §103(A)

Claims 48-91 remain rejected as being unpatentable over US 4,210,139 ("Higuchi") in view of US 5,980,927 ("Nelson"). This rejection is respectfully traversed as applied and as it may be applied to the claims as presently pending.

First, applicants note that the apparent error in the patent number that serves as the primary reference made in the earlier Office Action has been repeated in the present Office Action. Applicants assume that the Examiner intended the primary reference for this rejection to be US 4,210,139, and not US 4,412,139.

Second, applicants note that the Office has clarified the rejection. Applicants previously argued that the disclosures of Higuchi and Nelson could not be combined since Nelson discloses a solid implant

and Higuchi discloses an osmotic pump that delivers liquid formulation. In response, the Examiner stated:[1]

> **Nelson is relied upon for the solely teaching of fentanyl as a preferred highly potent analgesic suitable for prolonged delivery periods, and not relied upon for teaching any device or formulation.**

A prima facie case of obviousness can only be made if three basic criteria are met:

1) The prior art reference, or references when combined, ***must teach or suggest all the claim limitations***.[2]
2) There is some ***suggestion or motivation***, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.[3]
3) There must be a ***reasonable expectation of success***.[4]

All three criteria must be satisfied. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.[5] In the instant case, the Office has failed to establish a *prima facie* case of obviousness here for at least the following reasons.

The present claims require a combination of elements that is neither taught nor suggested by the disclosures of Higuchi and Nelson. Specifically:

- Claim 48 requires delivery of a composition comprising fentanyl or fentanyl congener for **48 hours or more** at a **low volume rate of 2 ml/day or less** and still provide sufficient analgesia in the subject. Claims 49-62 depend either directly or indirectly from claim 48 and thus include these same limitations.

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[1] Final Office Action, mailed March 20, 2006, page 6.

[2] *In re Royka*, 180 USPQ 580 (CCPA 1974).

[3] *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 21 USPQ2d 1941 (Fed. Cir. 1992).

[4] *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986).

- Claim 63 requires fentanyl or fentanyl congener be present in the composition at a **concentration of about 0.5 mg/ml to about 500 mg/ml or greater** *and* delivery at a **low volume rate of 2 ml/day or less**, and provide sufficient analgesia in the subject. Claims 64-83 depend either directly or indirectly from claim 63and thus include these same limitations.
- Claim 84 requires delivery of a composition comprising fentanyl or fentanyl congener for **48 hours or more** at **delivery rate of about 0.01 μg/hr to about 200 μg/hr**, and provide sufficient analgesia in the subject. Claims 85-91 depend either directly or indirectly from claim 48 and thus include these same limitations.

The methods of claims 48-91 require the delivery of an exceptionally small volume of a composition containing the fentanyl/fentanyl congener active agent , yet effective analgesia is achieved in the subject. As pointed out in the prior response, delivering such small volumes of drug is counter-intuitive, since logically it would be expected that the pharmacological effect of the drug would quickly drop off and become negligible well before one reached the low volume rate delivery as required by applicants' claims. Moreover, in the fields of pharmacology and pain management at the time of applicants' priority date, no highly concentrated fentanyl/fentanyl congener formulation was available nor was there any reasonable belief or expectation that one could be attained. As disclosed in applicants' specification, fentanyl/fentanyl congener formulations having a concentration that is substantially higher than conventional formulations have been invented by applicants, wherein the active agent can be present in up to 10,000 times or greater than the solubility of the fentanyl or fentanyl congener in aqueous solution.[6]

Applicants' ability to produce such formulations provided exceptional benefit to the art in that now, methods of pain management can be carried out by administering exceptionally small volumes of the fentanyl/fentanyl congener formulation to a site, avoiding accumulation of excessive drug at the

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[5] This motivation-suggestion-teaching test was most recently endorsed by the Federal Circuit in *In re Kahn* (Fed. Cir. 2006, 04–1616) (emphasizing the importance of the motivation-suggestion-teaching test for obviousness to avoid application of hindsight).

[6] See applicants' specification at page 18, second full paragraph through page 21, first full paragraph, and pages 35 and 36.

delivery site (pooling or depot effect) since the rate of administration is at or only slightly higher than the rate of removal of the drug from the delivery site.[7]

Turning to the cited art, Higuchi and Nelson ***fail to teach or suggest all of the limitations of the claims.*** The Office admits that neither Higuchi nor Nelson disclose all elements of the claims:[8]

> However, the combination of the references does not specifically teach the same delivery volume or the concentration of fentanyl in the device as claimed by applicant.

For this reason alone, the *prima facie* case must fall.

Neither Higuchi nor Nelson provides an enabling disclosure of the claimed invention to accomplish delivery of fentanyl or fentanyl congener as set out in the instant claims. The Federal Circuit recently stated that when considering motivation in an obviousness analysis, the problem examined is "not the specific problem solved by the invention but the general problem that confronted the inventor before the invention was made."[9] The Federal Circuit has recently reminded us that:

> "[a]lthough published subject matter is "prior art" for all that it discloses, ***in order to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention.***[10]

Higuchi and Nelson *fail to provide any disclosure of a formulation of fentanyl or fentanyl congener* (e.g., sufentanil) *of a sufficiently high concentration to achieve the delivery rates set out in the instant claims*. Neither Higuchi nor Nelson provides even a *single* fentanyl or fentanyl congener formulation. The Office, in fact, has acknowledged that Nelson does not provide any disclosure of a

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[7] See applicants specification at page 24, bottom paragraph.

[8] Final Office Action, mailed March 20, 2006, page 7.

[9] *In re Kahn* 441 F.3d 977; 2006 U.S. App. LEXIS 707 at page 19 (citations omitted).

[10] *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2006) (citing *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989)) (emphasis added).

formulation relevant to the instant claims, and has further not relied upon Nelson for disclosure of any formulation.

In order to overcome this basic defect in the rejection, the Office asserts that:[11]

> **The delivery volume and concentration of a fentanyl in the osmotic pump is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize according to individual patient condition. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal delivery volume and concentration of fentanyl in order to best achieve the desired results of pain relief.**

The claimed invention is not simply about manipulating delivery volumes and concentration of drug. Rather, the claims require the recited delivery rates and administration periods, and accordingly thus require use of a *concentrated* formulation of fentanyl or fentanyl congener. As the Office recognizes, these are *highly potent drugs*. Where a highly potent drug is to be administered, use of a concentrated formulation is not obvious. There is simply no teaching, motivation, or suggestion in Higuchi or Nelson use a concentrated formulation of fentanyl or fentanyl congener.

Withdrawal of this rejection is respectfully requested.

[11] Final Office Action, mailed March 20, 2006, page 7.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number DURE-007CON2.

Respectfully submitted,
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Date: June 20, 2006

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